L60 ANSWER 1 OF 9 MEDLINE on STN
TI High circulating **ghrelin**: a potential cause for hyperphagia and obesity in prader-willi syndrome.
TI High circulating **ghrelin**: a potential cause for hyperphagia and obesity in prader-willi syndrome.
SO The Journal of clinical endocrinology and metabolism, **(2002 Dec)** Vol. 87, No. 12, pp. 5461-4.
Journal code: 0375362. ISSN: 0021-972X.
AB . . . have GH deficiency and hypogonadotropic hypogonadism. The causes of the hyperphagia and abnormal GH secretion are unknown. To determine whether **ghrelin**, a novel GH secretagogue with orexigenic properties, is elevated in PWS, we measured fasting plasma **ghrelin** concentration; body **composition** (dual-energy x-ray absorptiometry); and subjective ratings of hunger (visual analog scale) in seven subjects (6 males and 1 female; age,. . . fasted overnight. All subjects were weight stable for at least 6 months before admission to the study. The mean plasma **ghrelin** concentration was higher in PWS than in the reference population (307 +/- 164 vs. 109 +/- 24 fmol/ml; P < 0.001), and this difference remained significant after adjustment for percentage body fat (P < 0.001). Plasma **ghrelin** was also higher (P = 0.0004) in PWS than in five healthy subjects fasted for 36 h. A positive correlation was found between plasma **ghrelin** and subjective ratings of hunger (r = 0.71; P = 0.008). Furthermore, in subjects with PWS, the concentration of the. . . hormone was not different before and after ingestion of 2 ml and a satiating amount of the same liquid meal (**ghrelin** concentrations: 307 +/- 164 vs. 306 +/- 205 vs. 260 +/- 134 fmol/ml, respectively; ANOVA for repeated measures, P = 0.56). This is the first evidence that **ghrelin**, a novel orexigenic hormone, is elevated in subjects with PWS. Our finding suggests that **ghrelin** may be responsible, at least in part, for the hyperphagia observed in PWS.
CT Check Tags: Female; Male
Adult
Eating: PH, physiology
Fasting: BL, blood
Humans
Hunger: PH, physiology
*Hyperphagia: ET, etiology
*Obesity: ET, etiology
Osmolar Concentration
*Peptide Hormones: BL, blood
Prader-Willi Syndrome: BL, blood
*Prader-Willi. . .
CN 0 (Peptide Hormones); 0 (**ghrelin**)

=> d ti kwic l60 all

L60 ANSWER 1 OF 9 MEDLINE on STN
TI High circulating **ghrelin**: a potential cause for hyperphagia and obesity in prader-willi syndrome.
TI High circulating **ghrelin**: a potential cause for hyperphagia and obesity in prader-willi syndrome.
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subjects were weight stable for at least 6 months before admission to the study. The mean plasma **ghrelin** concentration was higher in PWS than in the reference population (307 +/- 164 vs. 109 +/- 24 fmol/ml; P < 0.001), and this difference remained significant after adjustment for percentage body fat (P < 0.001). Plasma **ghrelin** was also higher (P = 0.0004) in PWS than in five healthy subjects fasted for 36 h. A positive correlation was found between plasma **ghrelin** and subjective ratings of hunger (r = 0.71; P = 0.008). Furthermore, in subjects with PWS, the concentration of the. . . hormone was not different before and after ingestion of 2 ml and a satiating amount of the same liquid meal (**ghrelin** concentrations: 307 +/- 164 vs. 306 +/- 205 vs. 260 +/- 134 fmol/ml, respectively; ANOVA for repeated measures, P = 0.56). This is the first evidence that **ghrelin**, a novel orexigenic hormone, is elevated in subjects with PWS. Our finding suggests that **ghrelin** may be responsible, at least in part, for the hyperphagia observed in PWS.

CT Check Tags: Female; Male
Adult
Eating: PH, physiology
Fasting: BL, blood
Humans
Hunger: PH, physiology
*Hyperphagia: ET, etiology
*Obesity: ET, etiology
Osmolar Concentration
*Peptide Hormones: BL, blood
Prader-Willi Syndrome: BL, blood
*Prader-Willi. . .

CN 0 (Peptide Hormones); 0 (**ghrelin**)

AN 2002705086 MEDLINE <<LOGINID::20060911>>

DN PubMed ID: 12466337

TI High circulating **ghrelin**: a potential cause for hyperphagia and obesity in prader-willi syndrome.

AU DelParigi Angelo; Tschop Matthias; Heiman Mark L; Salbe Arline D; Vozarova Barbora; Sell Susan M; Bunt Joy C; Tataranni P Antonio

CS Clinical Diabetes and Nutrition Section, National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases, Phoenix, Arizona 85016, USA.. adelpari@mail.nih.gov

NC DK056336 (NIDDK)

SO The Journal of clinical endocrinology and metabolism, **(2002 Dec)** Vol. 87, No. 12, pp. 5461-4.
Journal code: 0375362. ISSN: 0021-972X.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS Abridged Index Medicus Journals; Priority Journals

EM 200301

ED Entered STN: 17 Dec 2002
Last Updated on STN: 18 Jan 2003
Entered Medline: 17 Jan 2003

AB Prader-Willi syndrome (PWS) is a genetic disorder occurring in 1 of 10,000-16,000 live births and is characterized by excessive appetite with progressive massive obesity as well as short stature and mental retardation. Most patients have GH deficiency and hypogonadotropic hypogonadism. The causes of the hyperphagia and abnormal GH secretion are unknown. To determine whether **ghrelin**, a novel GH secretagogue with orexigenic properties, is elevated in PWS, we measured fasting plasma **ghrelin** concentration; body **composition** (dual-energy x-ray absorptiometry); and subjective ratings of hunger (visual analog scale) in seven subjects (6 males and 1 female; age, 26 +/- 7 yr; body fat, 39 +/- 11%, mean +/- SD) with PWS (diagnosis confirmed by genetic test) and 30 healthy subjects (reference population, 15 males and 15 females; age, 32 +/- 7 yr; body fat, 36 +/- 11%) fasted overnight. All subjects were weight stable for at least 6 months before admission to the

study. The mean plasma **ghrelin** concentration was higher in PWS than in the reference population (307 +/- 164 vs. 109 +/- 24 fmol/ml; P < 0.001), and this difference remained significant after adjustment for percentage body fat (P < 0.001). Plasma **ghrelin** was also higher (P = 0.0004) in PWS than in five healthy subjects fasted for 36 h. A positive correlation was found between plasma **ghrelin** and subjective ratings of hunger (r = 0.71; P = 0.008). Furthermore, in subjects with PWS, the concentration of the hormone was not different before and after ingestion of 2 ml and a satiating amount of the same liquid meal (**ghrelin** concentrations: 307 +/- 164 vs. 306 +/- 205 vs. 260 +/- 134 fmol/ml, respectively; ANOVA for repeated measures, P = 0.56). This is the first evidence that **ghrelin**, a novel orexigenic hormone, is elevated in subjects with PWS. Our finding suggests that **ghrelin** may be responsible, at least in part, for the hyperphagia observed in PWS.

CT Check Tags: Female; Male
Adult
Eating: PH, physiology
Fasting: BL, blood
Humans
Hunger: PH, physiology
*Hyperphagia: ET, etiology
*Obesity: ET, etiology
Osmolar Concentration
*Peptide Hormones: BL, blood
Prader-Willi Syndrome: BL, blood
*Prader-Willi Syndrome: CO, complications
Prader-Willi Syndrome: PP, physiopathology
Reference Values
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.

CN 0 (Peptide Hormones); 0 (**ghrelin**)

=> d ti kwic l60 1-9

L60 ANSWER 1 OF 9 MEDLINE on STN

TI High circulating **ghrelin**: a potential cause for hyperphagia and obesity in prader-willi syndrome.

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novel orexigenic hormone, is elevated in subjects with PWS. Our finding suggests that **ghrelin** may be responsible, at least in part, for the hyperphagia observed in PWS.

CT Check Tags: Female; Male
Adult
Eating: PH, physiology
Fasting: BL, blood
Humans
Hunger: PH, physiology
*Hyperphagia: ET, etiology
*Obesity: ET, etiology
Osmolar Concentration
*Peptide Hormones: BL, blood
Prader-Willi Syndrome: BL, blood
*Prader-Willi. . .

CN 0 (Peptide Hormones); 0 (**ghrelin**)

L60 ANSWER 2 OF 9 MEDLINE on STN

TI Fasting plasma **ghrelin** levels are negatively correlated with insulin resistance and PAI-1, but not with leptin, in obese children and adolescents.

TI Fasting plasma **ghrelin** levels are negatively correlated with insulin resistance and PAI-1, but not with leptin, in obese children and adolescents.

SO Diabetes, **(2002 Dec)** Vol. 51, No. 12, pp. 3408-11.
Journal code: 0372763. ISSN: 0012-1797.

AB **Ghrelin** is a novel growth hormone-releasing peptide isolated from human and rat stomach that induces weight gain by increasing food intake and reducing fat utilization. Although recent data indicate that **ghrelin** is downregulated in human adult obesity, the characteristics of human obesity are heterogeneous, especially in children and adolescents, and depend on the distribution of subcutaneous and visceral fat tissue. We measured fasting plasma **ghrelin** concentrations by radioimmunoassay in 49 obese Japanese children and adolescents (38 boys and 11 girls; mean age 10.2 +/- 2.8 years; BMI 28.0 +/- 4.5 kg/m(2), percent overweight 56.0 +/- 20.7%), and analyzed associations of their **ghrelin** concentrations with their body **composition**, insulin resistance, and adipocytokine concentrations. Fasting plasma **ghrelin** levels were negatively correlated with BMI and waist circumference, but not with percent overweight or percent body fat, whereas fasting. . . levels were positively correlated with all of the following parameters: BMI, waist circumference, percent overweight, and percent body fat. Plasma **ghrelin** levels were negatively correlated with fasting immunoreactive insulin, homeostasis model assessment insulin resistance index, and quantitative insulin sensitivity check index values. There was no correlation between plasma **ghrelin** and leptin, but **ghrelin** was negatively correlated with the PAI-1 concentrations. The results suggest that the downregulation of **ghrelin** secretion may be a consequence of higher insulin resistance associated with visceral fat accumulation and elevated PAI-1 concentrations, and not. . .

CT Check Tags: Female; Male
Adolescent
Adult
Body Composition
Child
*Fasting: BL, blood
Humans
***Insulin Resistance: PH, physiology**
Leptin: BL, blood
*Obesity: BL, blood
Obesity: PA, pathology
*Obesity: PP, physiopathology
*Peptide Hormones: BL, blood

*Plasminogen. . .
CN 0 (Leptin); 0 (Peptide Hormones); 0 (Plasminogen Activator Inhibitor 1); 0 (**ghrelin**)

L60 ANSWER 3 OF 9 MEDLINE on STN
TI Hypophysectomy prevents **ghrelin**-induced adiposity and increases gastric **ghrelin** secretion in rats.
TI Hypophysectomy prevents **ghrelin**-induced adiposity and increases gastric **ghrelin** secretion in rats.
SO Obesity research, **(2002 Oct)** Vol. 10, No. 10, pp. 991-9.
Journal code: 9305691. ISSN: 1071-7323.
AB OBJECTIVE: The novel gastric hormone **ghrelin** has recently been identified as an important modulator of energy homeostasis. Leptin-responsive hypothalamic neuropeptide Y/Agouti-related protein neurons are believed to mediate afferent **ghrelin** signals. Little is known, however, about **ghrelin**-induced efferent signals. We therefore investigated if hypothalamic-pituitary axes have a role in transferring **ghrelin**-induced changes of energy balance to the periphery. RESEARCH METHODS AND PROCEDURES: We subcutaneously injected hypophysectomized, as well as adrenalectomized, thyroidectomized, and sham-operated control rats with GH secretagogues [**ghrelin**, growth hormone (GH)-releasing peptide] for 1 week. Body weight, food intake, and body **composition** (chemical carcass analysis) were analyzed and compared with vehicle-treated controls. In addition, we quantified circulating levels of endogenous **ghrelin** in hypophysectomized and GH-treated normal rats. RESULTS: GH-secretagogue treatment of sham-operated control rats dose-proportionally increased food intake, body weight, and fat mass compared with vehicle-injected controls ($p < 0.01$). These effects, however, were not observed in **ghrelin** -treated hypophysectomized, thyroidectomized, or adrenalectomized rats, indicating an essential role for the pituitary axis in **ghrelin** -induced adiposity. Circulating levels of endogenous **ghrelin** were reduced by administration of GH in normal rats and were about 3-fold higher in hypophysectomized rats ($n = 20$, $p = 0.001$), suggesting a regulatory feedback loop involving the stomach and the pituitary to regulate gastric **ghrelin** secretion. DISCUSSION: According to these results, the endocrine pituitary is mediating **ghrelin** -induced changes toward a positive energy balance and is involved in the regulation of **ghrelin** secretion through a gastro-hypophyseal feedback loop.
CT Check Tags: Male
Adipose Tissue: ME, metabolism
***Adipose Tissue: PH, physiology**
Adrenalectomy
Animals
Body Weight: DE, drug effects
***Body Weight: PH, physiology**
Eating: DE, drug effects
Eating: PH, physiology
Growth Hormone: ME, metabolism
Growth Hormone: PD, pharmacology
Hypophysectomy
Hypothalamo-Hypophyseal System: DE, drug effects
Hypothalamo-Hypophyseal System: ME, metabolism
***Hypothalamo-Hypophyseal System: PH, physiology**
Insulin-Like Growth Factor I: PD, pharmacology
Oligopeptides: PD, pharmacology
Peptide Hormones: BL, blood
Peptide Hormones: ME, metabolism
*Peptide Hormones: PD, pharmacology
*Peptide Hormones: SE, secretion
Pituitary-Adrenal System: DE, drug effects
Pituitary-Adrenal System: ME, metabolism
***Pituitary-Adrenal System: PH, physiology**

Rats
Rats, Sprague-Dawley
Thyroidectomy
CN 0 (Oligopeptides); 0 (Peptide Hormones); 0 (**ghrelin**); 0 (growth hormone-releasing peptide-2)

L60 ANSWER 4 OF 9 MEDLINE on STN
TI Plasma **ghrelin** levels during exercise in healthy subjects and in growth hormone-deficient patients.
TI Plasma **ghrelin** levels during exercise in healthy subjects and in growth hormone-deficient patients.
SO European journal of endocrinology / European Federation of Endocrine Societies, **(2002 Jul)** Vol. 147, No. 1, pp. 65-70.
Journal code: 9423848. ISSN: 0804-4643.
AB OBJECTIVE: To characterise plasma levels of the recently identified endogenous ligand for the GH secretagogue receptor (**ghrelin**) during submaximal aerobic exercise in healthy adults and in GH-deficient adults. DESIGN: Eight healthy males (mean+/-s.e. age, 40.8+/-2.9 years) and. . . peak aerobic capacity (VO(2) peak) and lactate threshold (LT) on a cycle ergometer, as well as an evaluation of body **composition** . The patients were then studied on two occasions in random order when they exercised for 45 min at their LT.. . . after 45 min, whereas no increase was detected when exercising without GH (9.77+/-2.40 (GH) vs 0.11+/-0.07 microg/l (no GH)). Plasma **ghrelin** levels did not change significantly with time in either study, and no correlations were detected between **ghrelin** levels and parameters such as GH and IGF-I levels, age or body **composition**. Plasma **ghrelin** levels were significantly lower during the study period with GH as compared with the study with no GH. CONCLUSIONS: Submaximal aerobic exercise of an intensity sufficient to stimulate GH release was not associated with significant alterations in plasma **ghrelin** concentrations, which indicated that systemic **ghrelin** is not involved in the exercise-induced stimulation of GH secretion. The observation that **ghrelin** levels were lower during GH replacement suggests that GH may feedback-inhibit systemic **ghrelin** release.
CT Check Tags: Male
Adult
Anaerobic Threshold: PH, physiology
***Exercise: PH, physiology**
Human Growth Hormone: AD, administration & dosage
*Human Growth Hormone: DF, deficiency
Humans
*Hypopituitarism: BL, blood
Hypopituitarism: DT,. . .
CN 0 (Insulin-Like Growth Factor Binding Proteins); 0 (Peptide Hormones); 0 (Peptides); 0 (**ghrelin**)

L60 ANSWER 5 OF 9 MEDLINE on STN
TI Plasma **ghrelin** levels after diet-induced weight loss or gastric bypass surgery.
TI Plasma **ghrelin** levels after diet-induced weight loss or gastric bypass surgery.
SO The New England journal of medicine, **(2002 May 23)** Vol. 346, No. 21, pp. 1623-30.
Journal code: 0255562. E-ISSN: 1533-4406.
AB BACKGROUND: Weight loss causes changes in appetite and energy expenditure that promote weight regain. **Ghrelin** is a hormone that increases food intake in rodents and humans. If circulating **ghrelin** participates in the adaptive response to weight loss, its levels should rise with dieting. Because **ghrelin** is produced primarily by the stomach, weight loss after gastric bypass surgery may be accompanied by impaired **ghrelin** secretion. METHODS: We determined the 24-hour plasma **ghrelin** profiles, body **composition**, insulin levels, leptin levels, and insulin sensitivity in 13 obese subjects before

and after a six-month dietary program for weight loss. The 24-hour **ghrelin** profiles were also determined in 5 subjects who had lost weight after gastric bypass and 10 normal-weight controls; 5 of. . . in the dietary program were matched to the subjects in the gastric-bypass group and served as obese controls. RESULTS: Plasma **ghrelin** levels rose sharply shortly before and fell shortly after every meal. A diet-induced weight loss of 17 percent of initial body weight was associated with a 24 percent increase in the area under the curve for the 24-hour **ghrelin** profile (P=0.006). In contrast, despite a 36 percent weight loss after gastric bypass, the area under the curve for the **ghrelin** profile in the gastric-bypass group was 77 percent lower than in normal-weight controls (P<0.001) and 72 percent lower than in matched obese controls (P=0.01). The normal, meal-related fluctuations and diurnal rhythm of the **ghrelin** level were absent after gastric bypass. CONCLUSIONS: The increase in the plasma **ghrelin** level with diet-induced weight loss is consistent with the hypothesis that **ghrelin** has a role in the long-term regulation of body weight. Gastric bypass is associated with markedly suppressed **ghrelin** levels, possibly contributing to the weight-reducing effect of the procedure.

CT Check Tags: Female; Male
Adult
Appetite Regulation: PH, physiology
Body Composition
Circadian Rhythm
Comparative Study
Diet, Reducing
*Gastric Bypass
Humans
Insulin: BL, blood
Insulin Resistance
Leptin: BL, blood
Middle. . . Hormones
*Peptides: BL, blood
Postoperative Period
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, Non-P.H.S.
Research Support, U.S. Gov't, P.H.S.
***Weight Loss: PH, physiology**

CN 0 (Leptin); 0 (Peptide Hormones); 0 (Peptides); 0 (**ghrelin**)

L60 ANSWER 6 OF 9 MEDLINE on STN

TI **Ghrelin**, macronutrient intake and dietary preferences in long-evans rats.

TI **Ghrelin**, macronutrient intake and dietary preferences in long-evans rats.

SO Biochemical and biophysical research communications, **(2002 Apr 12)** Vol. 292, No. 4, pp. 1031-5.
Journal code: 0372516. ISSN: 0006-291X.

AB **Ghrelin** is a recently discovered peptide that is primarily produced by the stomach. As a ligand of the growth hormone (GH). . . and has adipogenic effects in rodents. Although its circulating levels are modulated by fasting and refeeding, its relationship with diet **composition** is not known. In the present paper, we measured plasma **ghrelin** as well as two important hormones (leptin and insulin) in Long-Evans rats placed in two different feeding situations, e.g., either. . . their fat or carbohydrate preference. The intake of the HF diet for 14 weeks was associated with lower levels of **ghrelin** (-30% vs control diet; P < 0.01). These levels increased when the percentage of carbohydrate in the diet increased (+26 to +42% vs control diet; P < 0.01 or less). **Ghrelin** was inversely correlated with plasma leptin (r = -0.55; P < 0.003) and blood glucose (r = -0.58; P <. . . sampling of specific fat pads (r = -0.62; P < 0.0001). In the food choice experiment, fat-preferring rats had plasma

ghrelin levels lower than the carbohydrate-preferring rats (-33%; P < 0.0002). **Ghrelin** secretion was therefore very sensitive to the diet **composition**. Its down-regulation by fat ingestion might serve as a counterregulatory mechanism to limit the development of dietary-induced adiposity. **Ghrelin** may signal when a high calorie diet is ingested.

CT Check Tags: Male
Animals
Blood Glucose
Body Weight: DE, drug effects
Body Weight: PH, physiology
Choice Behavior: PH, physiology
Dietary Carbohydrates: PD, pharmacology
Dietary Fats: PD, pharmacology
Down-Regulation
***Eating: PH, physiology**
Energy Intake: PH, physiology
Food Preferences: DE, drug effects
***Food Preferences: PH, physiology**
*Insulin: BL, blood
*Leptin: BL, blood
*Peptide Hormones
*Peptides: BL, blood
Peptides: SE, secretion
Rats
Rats, Long-Evans

. . .

CN 0 (Blood Glucose); 0 (Dietary Carbohydrates); 0 (Dietary Fats); 0 (Leptin); 0 (Peptide Hormones); 0 (Peptides); 0 (**ghrelin**)

L60 ANSWER 7 OF 9 MEDLINE on STN

TI GH-releasing peptide-2 increases fat mass in mice lacking NPY: indication for a crucial mediating role of hypothalamic agouti-related protein.

SO Endocrinology, **(2002 Feb)** Vol. 143, No. 2, pp. 558-68.
Journal code: 0375040. ISSN: 0013-7227.

AB **Ghrelin**, an endogenous GH secretagogue, is capable of stimulating adiposity in rodents. Because such adiposity was thought to be mediated by hypothalamic NPY neurons, we investigated by which mechanism a synthetic **ghrelin** receptor agonist, GHRP-2, would generate a positive energy balance in NPY-deficient [Npy(-/-) mice] and wild-type controls. A dose-dependent increase in body weight and food intake was observed during daily sc injections with GHRP-2. Pre- and posttreatment analysis of body **composition** indicated increased fat mass and bone mass but not lean mass. Respiratory quotient was increased in GHRP-2-treated mice, indicating preservation. . . AGRP action by melanocortin-receptor agonist MT-II prevented GHRP-induced weight gain in Npy(-/-) mice. In conclusion, chronic peripheral treatment with a **ghrelin** receptor agonist induced a positive energy balance leading to fat gain in the absence of NPY. These effects could be mediated in part by AGRP. To date, there are few therapeutics that can produce a positive energy balance. **Ghrelin** receptor agonists offer a treatment option for syndromes like anorexia nervosa, cancer cachexia, or AIDS wasting.

CT Check Tags: Male
Adipose Tissue: DE, drug effects
***Adipose Tissue: PH, physiology**
Animals
Body Weight: DE, drug effects
Bone Development: DE, drug effects
Calorimetry, Indirect
Chromatography, High Pressure Liquid
Densitometry, X-Ray
Eating: DE, drug effects

Genotype
Hormones: BL, blood
***Hypothalamus: PH, physiology**
Mice
Mice, Knockout
Neuropeptide Y: GE, genetics
***Neuropeptide Y: PH, physiology**
*Oligopeptides: PD, pharmacology
***Proteins: PH, physiology**
Receptors, Cell Surface: AG, agonists
***Receptors, Cell Surface: PH, physiology**
Receptors, Corticotropin: AG, agonists
*Receptors, G-Protein-Coupled
Receptors, Melanocortin
Reverse Transcriptase Polymerase Chain Reaction

L60 ANSWER 8 OF 9 MEDLINE on STN
TI **Ghrelin** causes hyperphagia and obesity in rats.
TI **Ghrelin** causes hyperphagia and obesity in rats.
SO Diabetes, **(2001 Nov)** Vol. 50, No. 11, pp. 2540-7.
Journal code: 0372763. ISSN: 0012-1797.
AB **Ghrelin**, a circulating growth hormone-releasing peptide derived from the stomach, stimulates food intake. The lowest systemically effective orexigenic dose of **ghrelin** was investigated and the resulting plasma **ghrelin** concentration was compared with that during fasting. The lowest dose of **ghrelin** that produced a significant stimulation of feeding after intraperitoneal injection was 1 nmol. The plasma **ghrelin** concentration after intraperitoneal injection of 1 nmol of **ghrelin** (2.83 +/- 0.13 pmol/ml at 60 min postinjection) was not significantly different from that occurring after a 24-h fast (2.79 +/- 0.32 pmol/ml). After microinjection into defined hypothalamic sites, **ghrelin** (30 pmol) stimulated food intake most markedly in the arcuate nucleus (Arc) (0-1 h food intake, 427 +/- 43% of. . . 0.01 vs. all other nuclei), which is potentially accessible to the circulation. After chronic systemic or intracerebroventricular (ICV) administration of **ghrelin** for 7 days, cumulative food intake was increased (intraperitoneal **ghrelin** 13.6 +/- 3.4 g greater than saline-treated, P < 0.01; ICV **ghrelin** 19.6 +/- 5.5 g greater than saline-treated, P < 0.05). This was associated with excess weight gain (intraperitoneal **ghrelin** 21.7 +/- 1.4 g vs. saline 10.6 +/- 1.9 g, P < 0.001; ICV **ghrelin** 15.3 +/- 4.3 g vs. saline 2.2 +/- 3.8 g, P < 0.05) and adiposity. These data provide evidence that **ghrelin** is important in long-term control of food intake and body weight and that circulating **ghrelin** at fasting concentrations may stimulate food intake.
CT Check Tags: Male
Animals
Body Composition: DE, drug effects
Body Weight: DE, drug effects
Drug Administration Schedule
Eating: DE, drug effects
Fasting: BL, blood
Hormones: BL, blood
*Hyperphagia: CI, chemically induced
Hypothalamus: PH, physiology
Injections, Intraperitoneal
Injections, Intraventricular
*Obesity: CI, chemically induced
*Peptide Hormones
*Peptides
Peptides: AD, administration & dosage
Peptides:. . .
CN 0 (Hormones); 0 (Peptide Hormones); 0 (Peptides); 0 (**ghrelin**)

L60 ANSWER 9 OF 9 MEDLINE on STN

TI Plasma **ghrelin** concentration and energy balance: overfeeding and negative energy balance studies in twins.

TI Plasma **ghrelin** concentration and energy balance: overfeeding and negative energy balance studies in twins.

SO The Journal of clinical endocrinology and metabolism, **(2001 Sep)** Vol. 86, No. 9, pp. 4547-51.
Journal code: 0375362. ISSN: 0021-972X.

AB Central (intracerebral ventral) and peripheral (subcutaneous and intraperitoneal) administration of **ghrelin** causes obesity in rodents by increasing food intake and decreasing fat oxidation. Recent studies in humans have shown that plasma **ghrelin** concentration was inversely related to body fat and was lower in Pima Indians, a population susceptible to obesity. Whether **ghrelin** plays a role in the etiology of obesity in humans is unknown. We, therefore, measured plasma **ghrelin** concentration before and after two interventions in monozygotic twins previously studied at Laval University, Quebec City. Twelve pairs of monozygotic. . . a 53,000 kcal negative energy balance induced by exercise over a 93-day period. At baseline, for all the subjects, plasma **ghrelin** concentration was negatively correlated with body mass and body fatness (r varying from 0.36 to 0.45). The intraclass coefficient for the twin resemblance (r(I) = 0.75; p = 0.006) indicated that plasma **ghrelin** concentration is a familial trait. In response to the 100-day intervention, plasma **ghrelin** exhibited a non-significant decrease of 61 +/- 30 fmol/l (p = 0.18) with overfeeding and a non-significant increase of 58 +/- 34 fmol/l (p = 0.17) with negative energy balance. However, there was no relationship between baseline plasma **ghrelin** concentration and the magnitude of body weight change in both interventions. These first experimental data under "clamped energy balance conditions" do not provide evidence that plasma **ghrelin** is involved in the etiology of human obesity. However, studies in free-living individuals are needed to clarify this question.

CT Check Tags: Female; Male
Adipocytes: PH, physiology
Adipose Tissue: CY, cytology
Adipose Tissue: DE, drug effects
Adult
Body Composition: GE, genetics
Body Composition: PH, physiology
Body Weight: GE, genetics
***Body Weight: PH, physiology**
Cell Size: GE, genetics
Cell Size: PH, physiology
Eating: PH, physiology
Energy Metabolism: GE, genetics
***Energy Metabolism: PH, physiology**
Humans
Insulin: BL, blood
*Peptide Hormones
*Peptides: BL, blood
Peptides: GE, genetics

CN 0 (Peptide Hormones); 0 (Peptides); 0 (**ghrelin**)

L73 ANSWER 1 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2006:295972 CAPLUS
DOCUMENT NUMBER: 144:344629
TITLE: Virus-like particles comprising a fusion protein of the coat protein of bacteriophage AP205 and an antigenic polypeptide which have use for peptide display and vaccines
INVENTOR(S): Bachmann, Martin; Tissot, Alain; Jennings, Gary; Renhofa, Regina; Pumpens, Paul; Cielens, Indulis
PATENT ASSIGNEE(S): Cytos Biotechnology AG, Switz.
SOURCE: PCT Int. Appl., 73 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006032674	A1	20060330	WO 2005-EP54721	20050921

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

PRIORITY APPLN. INFO.: US 2004-611308P P 20040921
EP 2005-105229 A 20050614

AB The present invention is based on the discovery that a large variety of polypeptides can be fused to the N- or C-terminus of the coat protein of bacteriophage AP205 and the resulting fusion proteins form virus-like particles (VLPs) when expressed in a host, typically and preferably in Escherichia coli. Furthermore, if the polypeptide comprises at least one antigen, the antigen or at least one antigenic site of the antigen is displayed on the outer surface of the assembled VLPs. For example, a fusion protein comprising the coat protein of AP205 and a highly **hydrophobic** T-cell epitope, the p33 epitope, forms virus-like particles, whereas an analogous fusion with the cost protein of phage fr fails to form VLPs. The modified VLP disclosed in the present invention is useful in the production of compns. for inducing immune responses for the **prevention** or treatment of diseases, disorders including infectious diseases, allergies, cancers, and drug addiction. The modified VLP disclosed in the present invention is, in particular, useful to efficiently induce self-specific immune responses, in particular antibody responses.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L73 ANSWER 2 OF 4 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2005-31217 BIOTECHDS
TITLE: New pharmaceutical composition comprising an isolated binding member comprising a binding domain that binds to a secretagogue compound, useful for treating a disorder of appetite regulation associated with e.g., cachexia; involving vector-mediated gene transfer and expression in host cell for therapy
AUTHOR: HANSEN C

PATENT ASSIGNEE: GASTROTECH PHARMA AS
PATENT INFO: WO 2005097831 20 Oct 2005
APPLICATION INFO: WO 2005-DK241 7 Apr 2005
PRIORITY INFO: DK 2004-574 7 Apr 2004; DK 2004-574 7 Apr 2004
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2005-747302 [76]
AN 2005-31217 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - A pharmaceutical composition comprising an isolated binding member comprising at least one binding domain capable of specifically binding to a secretagogue compound with a dissociation constant Kd for the secretagogue compound that is less than 1x10-4 M, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) detecting a disorder in appetite regulation in an individual; (2) a kit for detecting a disorder in appetite regulation in an individual, comprising at least one binding member that is labelled; (3) treating an individual; (4) an isolated nucleic acid molecule encoding at least a part of the binding member; (5) a vector comprising the nucleic acid molecule; (6) a host cell comprising the nucleic acid; and (7) a cell line engineered to express the binding member.

BIOTECHNOLOGY - Preferred Composition: The pharmaceutical composition comprises an isolated binding member comprising at least one binding domain capable of specifically binding to a secretagogue compound with a dissociation constant Kd for the secretagogue compound that is less than 1x10-4 M. The binding domain is capable of specifically binding **ghrelin**. The isolated binding member is a pure isolated binding member. The binding member comprises antibodies or other immunologically active molecules. The antibodies comprise monoclonal antibodies, polyclonal antibodies or a mixture of monoclonal antibodies. The active fragment of antibodies are Fab, Fab', F(ab)2 or Fv. The binding member is an affibody or a mixture of affibodies. The binding member is an antibody affibody chimera. The immunologically active molecule is a mixture of antibody affibody chimeras. The pharmaceutical composition comprises at least two different binding members. The binding member binds to an epitope on the secretagogue, the epitope being residues 1-15, 2-16, 16-25, 17-25, 16-23 or 18-25 of the fully defined 28-amino acid sequence (SEQ ID NO: 1). The binding member is capable of prolonging the plasma half-life of a secretagogue compound within an individual. The prolonging of the plasma half-life is caused by binding of the binding member to the secretagogue compound. The binding member comprises 2 binding sites. The pharmaceutical composition further comprises a secretagogue compound. The secretagogue is **ghrelin** or **ghrelin**-like compound or its salt. The **ghrelin**-like compound comprises a structure of the formula (I) comprising: Z1 - (X1)m - (X2) - (X3)n - Z2. Z1 = is an optionally present protecting group; X1 = is an amino acid, which is naturally occurring or synthetic; may be modified by a bulky **hydrophobic** group, preferably C1-C35 acyl group, or a fatty acid; X2 = is any naturally occurring or synthetic amino acid, which is modified with a bulky **hydrophobic** group, preferably C1-C35 acyl group, or a fatty acid; preferably, a modified Ser, Cys or Lys; X3 = is any naturally occurring or synthetic amino acid; may be modified by a bulky **hydrophobic** group, preferably C1-C35 acyl group, or a fatty acid; Z2 = is an optionally present protecting group; m = is an integer in the range of 1-10, 1-9, 1-8, 1-7, 1-6, 1-5, 1-4, 1-3 or 1-2, or 2; n = is 0 or an integer in the range of 1-35, 1-25, 1-24, 1-15, 1-10, 10-25, 10-24, 15-25 or 15-24. The **ghrelin**-like compound comprises: (a) formula (II) comprising Z1 - Gly - (X1)m-1 - (X2) - (X3)n - Z2; (b) formula (III) comprising Z1 - Gly - Ser - (X2) - (X3)n - Z2; or (c) Z1 - Gly - (X2) - (X3)n - Z2. Preferably, the **ghrelin**-like compound comprises formula (III) comprising Z1 - Gly - Ser - (X2) - (X3)n - Z2. (X3)n = comprises the sequence Phe-Leu-Ser-Pro-Glu-His-Gln; Phe-Leu-Ser-Pro-Glu-His; Phe-Leu-Ser-Pro-Glu; Phe-Leu-Ser-Pro; Phe-Leu-Ser; Phe-Leu; or Phe. The pharmaceutical composition further

comprises a carrier or diluent. The pharmaceutical composition is formulated for parenteral, nasal, pulmonary or subcutaneous administration. The composition is administered in unit dosage form comprising 5-250 mg of the binding member. The pharmaceutical composition is administered in combination with a stomach-derived factor. The stomach-derived factor is **ghrelin** or a **ghrelin**-like compound. The pharmaceutical composition is useful for treating a disorder of appetite regulation caused by, or associated with one or more of cachexia, a neoplastic disorder such as cancer, or AIDS-related cachexia, a pathological disorder associated with **ghrelin** deficiency, or a loss of body fat or bone mass in a gastrectomized individual. Preferred Vector: The vector comprises a nucleotide sequence that regulates the expression of the binding member encoded by the nucleic acid molecule. Preferred Method: Detecting a disorder in appetite regulation in an individual comprises: (a) providing a biological sample from the individual; (b) adding at least one binding member to the biological sample; and (c) detecting the binding members bound to the biological sample, thereby detecting or diagnosing the disease or disorder. Treating an individual comprises administering the pharmaceutical composition. The individual is suffering from a disorder of appetite regulation caused by, or associated with one or more of cachexia, a neoplastic disorder such as cancer, or AIDS-related cachexia, or a pathological disorder associated with **ghrelin** deficiency. The individual is a gastrectomized individual suffering from a loss of body fat or bone mass. The treatment comprises improving the sense of well-being and the quality of life in the individual. The treatment stimulates appetite and **prevents** malnutrition of the individual.

ACTIVITY - Eating-Disorders-Gen; Anabolic. No biological data given.

MECHANISM OF ACTION - Secretagogue inhibitor.

USE - The isolated binding member is useful for producing the pharmaceutical composition for treating a disorder of appetite regulation caused by, or associated with cachexia, a neoplastic disorder such as cancer, or AIDS-related cachexia, or a pathological disorder associated with **ghrelin** deficiency; or a loss of body fat or bone mass in a gastrectomized individual (claimed).

ADMINISTRATION - Dosage comprises 0.1-10 mg/kg/day. The pharmaceutical composition is administered via parenteral, nasal, pulmonary or subcutaneous route. (All claimed.)

EXAMPLE - No relevant examples given.(167 pages)

L73 ANSWER 3 OF 4 BIOTECHDS COPYRIGHT 2006 THE THOMSON CORP. on STN
ACCESSION NUMBER: 2005-24153 BIOTECHDS
TITLE: Producing a biologically active fusion protein such as insulin or growth hormone comprises expressing in a plant a nucleic acid sequence encoding a glycosylation site and at least one biologically active protein;
involving vector-mediated gene transfer and expression in host cell for therapy
AUTHOR: KIELISZEWSKI M J; XU J; KOPCHICK J; OKADA S
PATENT ASSIGNEE: UNIV OHIO STATE
PATENT INFO: WO 2005069845 4 Aug 2005
APPLICATION INFO: WO 2005-US1160 14 Jan 2005
PRIORITY INFO: US 2004-602562 18 Aug 2004; US 2004-536486 14 Jan 2004
DOCUMENT TYPE: Patent
LANGUAGE: English
OTHER SOURCE: WPI: 2005-564058 [57]
AN 2005-24153 BIOTECHDS
AB DERWENT ABSTRACT:

NOVELTY - Producing (M1) a biologically active fusion protein, comprises expressing in a plant at least one nucleic acid sequence encoding at least one glycosylation site and at least one biologically active protein, as a glycoprotein, where the molecular weight of the glycoprotein is greater than or equal to 10 kD, and where the

carbohydrate component of the glycoprotein accounts for greater than or equal to 10% of the molecular weight of the glycoprotein.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for: (1) a nucleic acid construct (I) for expression of at least one biologically active protein in plants, comprising at least one nucleic acid sequence encoding a glycosylation site and at least one nucleic acid sequence encoding a biologically active protein; (2) a plant-derived biologically active mammalian fusion glycoprotein (PFP), comprising at least one glycomodule, covalently linked to a mammalian biologically active protein; (3) increasing (M2) the aqueous solubility of a protein molecule, by preparing a nucleic acid sequence encoding at least one glycosylation site and at least one protein, and expressing the nucleic acid construct as a fusion glycoprotein, where the carbohydrate component of the glycoprotein accounts for greater than or equal to 10% of the molecular weight of the glycoprotein; (4) an injectable pharmaceutical formulation (II), comprising glycosylated human growth hormone, and excluding at least one excipient chosen from mannitol, sorbitol, trehalose, glucose, glycine, leucine, trileucine, histidine, and phospholipid; (5) a lyophilized powder formulation (III) of glycosylated human growth hormone exhibiting a solubility of greater than or equal to 10 mg/ml, where the formulation excludes at least one excipient chosen from mannitol, sorbitol, trehalose, glucose, glycine, leucine, trileucine, histidine, and phospholipid; (6) increasing (M3) the yield in plant production of a protein, comprising preparing a nucleic acid construct comprising at least one signal peptide nucleic acid coding sequence, at least one glycosylation site nucleic acid coding sequence, and at least one protein nucleic acid coding sequence, and expressing the nucleic acid construct as a glycoprotein; (7) a protein (IV) produced by (M3); (8) a human growth hormone molecule (V) covalently attached to an amino acid sequence comprising at least one glycomodule, where the glycomodule is chosen from: (a) X-Hypn or X-Pro-Hypn, where n is 4-100; (b) Hypn-X, where n is from 4-100; (c) (Hyp-X)n, where n is 4-100; and (d) (X-Hyp)n, where n is 4-100, where X is any amino acid in the glycomodule X-Pro-Hypn, and where X is chosen from Ser, Ala, Thr, and Val for the glycomodules X-Hypn, Hypn-X, (Hyp-X)n, and (X-Hyp)n; (9) a human growth hormone antagonist molecule (VI) covalently attached to an amino acid sequence comprising at least one glycomodule, as described in (V); (10) treating (M4) a patient suffering from growth hormone deficiency or insufficiency by administering glycosylated human growth hormone (preferably V); (11) treating (M5) a patient suffering from excess human growth hormone or growth hormone activity by administering a glycosylated growth hormone antagonist (preferably VI); (12) treating (M6) a patient suffering from type I or type II diabetes, by administering glycosylated insulin; (13) **preventing** (M7) allergic immune response in a mammal by performing at least one administration of a plant-derived fusion glycoprotein comprising at least one glycomodule covalently linked to a biologically active protein, where the glycomodule is chosen from X-Hypn and X-Pro-Hypn, where n is 2-1000, and X is any amino acid (preferably Lys, Ser, Ala, Thr, Gly or Val); and (14) increasing (M8) the half-life of a biologically active fusion protein, by expressing in a plant at least one nucleic acid sequence encoding at least one glycosylation site and at least one biologically active protein as a glycoprotein, where the molecular weight of the glycoprotein is greater than or equal to 10 kD, and where the carbohydrate component of the glycoprotein accounts for greater than or equal to10% of the molecular weight of the glycoprotein.

BIOTECHNOLOGY - Preferred Method: In (M1) the biologically active fusion protein is selected from insulin, insulin-like growth factor, somatostatin, growth hormone releasing hormone, **ghrelin**, prolactin, placental lactogen, growth hormone, and growth hormone antagonist. The molecular weight of the glycoprotein is greater than or equal to35, 40, or 45 kD. The pharmacokinetic half-life of the glycoprotein is greater than that of a corresponding wild-type protein. The at least one glycosylation site is chosen from: (a) X-Pron or Pron-X,

where n is 6-100; and (b) (X-Pro)n or (Pro-X)n, where n is 6-100. X can be any amino acid, but is preferably Lys, Ser, Ala, Thr, Gly or Val, most preferably Ser, Ala, Thr, or Val. The biologically active protein is (human) growth hormone and the glycoprotein comprises (Ser-Hyp)10, which is preferably covalently attached to the C-terminus of the growth hormone. In (M2) the carbohydrate content of the glycoprotein accounts for greater than or equal to50, 75 or 90% of the molecular weight of the glycoprotein. In (M3) the glycosylation sites are preferably as described above for (M1), except that for (a) n is 2-1000, and for (b) it is 1-1000. The nucleic acid construct excludes a sequence encoding green fluorescent protein. In (M6) the glycosylated insulin preferably comprises at least one glycomodule as described for (V). In (M8) the glycosylation site is preferably as described for (M1). Preferred Protein: In the plant-derived biologically active mammalian fusion protein the glycomodule is preferably within the interior of the protein. The protein is chosen from growth hormone, growth hormone antagonists, growth hormone releasing hormone, somatostatin, **ghrelin**, leptin, prolactin, monocyte chemoattractant protein-1, interleukin-10, pleiotropin, interleukin-7, interleukin-8, interferon omega, interferon-alpha2, interferon gamma, interleukin-1, fibroblast growth factor 6, IFG-1, insulin-like growth factor I, insulin, erythropoietin, granulocyte macrophages-colony stimulating factor (GMCSF), and any humanized monoclonal antibody, where the glycomodule comprises X-Hypn, X-Pro-Hypn, or Hypn-X, where n is 2-1000, and (X-Hyp)n or (Hyp-X)n, where n is 1-1000, and where X is any amino acid as described above. The biologically active mammalian protein is a human protein. The glycomodule comprises (X-Hyp)n or (Hyp-X)n, where X is chosen from Lys, Ser, Ala, Thr, Gly and Val. The protein is human growth hormone, and the glycomodule comprises (Ser-Hyp)10. The fusion glycoprotein is covalently linked to at least one carbohydrate molecule.

ACTIVITY - Antidiabetic; Endocrine-Gen.; Osteopathic; Anorectic; Cytostatic; Antiallergic. No biological data given.

MECHANISM OF ACTION - Hormone agonist; Hormone antagonist.

USE - (M1) is useful for producing a biologically active fusion protein. The biologically active mammalian protein is chosen from insulin, insulin-like growth factor, somatostatin, growth hormone releasing hormone, **ghrelin**, prolactin, placental lactogen, growth hormone, and growth hormone antagonist. (M4) is useful for treating a patient suffering from growth hormone deficiency. (M5) is useful for treating a patient suffering from excess growth hormone activity. (M6) is useful for treating a patient suffering from type I or type II diabetes. (M7) is useful for **preventing** an allergic immune response in a mammal. (All claimed). The glycosylated growth hormone (V) can be used to treat conditions such as osteoporosis, bone fractures, Turner's syndrome and cancers, to increase meat production and carcass quality in e.g., chickens, sheep, pigs, cattle and fish, and to increase milk production in dairy cattle.

ADMINISTRATION - (VI) is administered orally, rectally, transdermally, intravenously, subcutaneously or intramuscularly, at a dose of 0.1-10 mg/day, preferably 1 mg/day.

ADVANTAGE - The pharmacokinetic half-life of the glycoprotein is greater than that of a corresponding wild-type protein. The glycoprotein produced by (M1) has increased solubility, increased resistance to proteolytic enzymes and increased stability.

EXAMPLE - Human growth hormone cDNA was produced by RT-PCR from the total RNA extracted from mouse L-cells stably transfected with hGH gene using the following primer set: 5'- ACCCGGGCCTTCCCAACCATTCCCTTATCC-3' and 5'-GATTCCATGGTGAAGCCACAGCTGCCCTCCAC-3'. The resulting PCR fragment contained the open reading frame for hGH but lacked its signal peptide. This fragment was cloned into pUC-SS(tob)-EGFP as an XmaI/NcoI fragment between SS(tob), which encodes the extensin signal sequence (SS) from tobacco, and the gene for enhanced green fluorescent protein (EGFP) to generate the plasmid designed pUC-SS(tob)-hGH-EGFP. The synthetic gene encoding ten repeats of the dipeptide Ser-Pro (SP)10 was constructed by

primer extension of two mutually priming oligonucleotide. The (SP)10 gene was subcloned into pUC-SS(tob)-hGH-EGFP as a NcoI and BsrGI fragment, replacing EGFP to generate pUC-SS(tab)-hGH-(SP)10. Plasmid pBI-SS(tob)-hGH-(SP)10 was introduced into Agrobacterium tumefaciens strain LBA4404, then suspension-cultured tobacco cells (Nicotiana tabacum, BY2) were transformed with the Agrobacterium. Cells were grown in liquid SH medium comprised of the same components as above, except excluding TIMENTIN. The medium from transformed cells was harvested after 8-10 days of culture. The cells were centrifuged, and the supernatant was fractionated by **hydrophobic** interaction chromatography, to obtain hGH-(SO)10 fusion glycoprotein.(182 pages)

L73 ANSWER 4 OF 4 CAPLUS COPYRIGHT 2006 ACS on STN
ACCESSION NUMBER: 2005:1291998 CAPLUS
DOCUMENT NUMBER: 144:40803
TITLE: Vasoactive kit and compositions comprising emollients and polymeric additive
INVENTOR(S): Friedman, Doron; Besonov, Alex; Tamarkin, Dov; Eini, Meir
PATENT ASSIGNEE(S): Foamix Ltd., Israel
SOURCE: U.S. Pat. Appl. Publ., 18 pp., Cont.-in-part of U.S. Ser. No. 911,367.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 12
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2005271596	A1	20051208	US 2005-124676	20050509
WO 2004037225	A2	20040506	WO 2003-IB5527	20031024
WO 2004037225	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2005069566	A1	20050331	US 2004-911367	20040804

PRIORITY APPLN. INFO.:

IL 2002-152486	A	20021025
US 2002-429546P	P	20021129
US 2003-492385P	P	20030804
WO 2003-IB5527	W	20031024
US 2004-911367	A2	20040804

AB The present invention relates to a therapeutic kit to provide an effective dosage of a vasoactive agent, including an aerosol packaging assembly with a container accommodating a pressurized product; and an outlet capable of releasing the pressurized product as a foam. The pressurized product comprises a foamable composition including: a vasoactive agent; a carrier selected from the group consisting of a **hydrophobic** organic carrier, an organic polar solvent, an emollient and mixts. thereof at 2-50% by weight, a surfactant, 0.01-5% by weight of at least 1 polymeric additive selected from the group consisting of a bioadhesive agent, a gelling agent, a film forming agent and a phase change agent, water; and liquefied or compressed gas propellant at a concentration of 3-25% by weight of the total composition

L89 ANSWER 1 OF 5 MEDLINE on STN
ACCESSION NUMBER: 2002721798 MEDLINE <<LOGINID::20060911>>
DOCUMENT NUMBER: PubMed ID: 12484464
TITLE: Identification and localization of the fatty **acid** modification in **ghrelin** by electron capture dissociation.
AUTHOR: Guan Ziqiang
CORPORATE SOURCE: Molecular Profiling Proteomics, Merck Research Laboratories, Rahway, New Jersey 07065, USA.. ziqiang_guan@merck.com
SOURCE: Journal of the American Society for Mass Spectrometry, **(2002 Dec)** Vol. 13, No. 12, pp. 1443-7. Journal code: 9010412. ISSN: 1044-0305.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200301
ENTRY DATE: Entered STN: 18 Dec 2002
Last Updated on STN: 7 Jan 2003
Entered Medline: 6 Jan 2003

AB Electron capture dissociation (ECD) has been demonstrated to be an effective fragmentation technique for characterizing the site and structure of the fatty **acid** modification in **ghrelin**, a 28-residue growth-hormone-releasing peptide that has an unusual ester-linked n-octanoyl (C8:0) modification at Ser-3. ECD cleaves 21 of 23 possible backbone amine bonds, with the product ions (c and z* ions) covering a greater amino **acid** sequence than those obtained by collisionally activated dissociation (CAD). Consistent with the ECD nonergodic mechanism, the ester-linked octanoyl group is retained on all backbone cleavage product ions, allowing for direct localization of this labile modification. In addition, ECD also induces the ester bond cleavage to cause the loss of octanoic **acid** from the **ghrelin** molecular ion; the elimination process is initiated by the capture of an electron at the protonated ester group, which is followed by the radical-site-initiated reaction known as alpha-cleavage. The chemical **composition** of the attached fatty **acid** can be directly obtained from the accurate Fourier transform ion cyclotron resonance (FTICR) mass measurement of the ester bond cleavage product ions.

L89 ANSWER 2 OF 5 MEDLINE on STN
ACCESSION NUMBER: 2002298502 MEDLINE <<LOGINID::20060911>>
DOCUMENT NUMBER: PubMed ID: 12031959
TITLE: Central leptin gene therapy blocks high-fat diet-induced weight gain, hyperleptinemia, and hyperinsulinemia: increase in serum **ghrelin** levels.
AUTHOR: Dube Michael G; Beretta Elena; Dhillon Harveen; Ueno Naohiko; Kalra Pushpa S; Kalra Satya P
CORPORATE SOURCE: Department of Physiology and Functional Genomics, University of Florida McKnight Brain Institute, College of Medicine, Gainesville, Florida 32610-0244, USA.
CONTRACT NUMBER: DK-37273 (NIDDK)
NS32727 (NINDS)
SOURCE: Diabetes, **(2002 Jun)** Vol. 51, No. 6, pp. 1729-36. Journal code: 0372763. ISSN: 0012-1797.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 2 Jun 2002
Last Updated on STN: 25 Jun 2002
Entered Medline: 24 Jun 2002

AB Recombinant adeno-associated virus (rAAV), encoding either rat leptin (rAAV-lep) or green fluorescent protein (rAAV-GFP, control), was injected intracerebroventricularly in rats consuming a high-fat diet (HFD; 45 kcal%). Caloric consumption and body weight were monitored weekly until the rats were killed at 9 weeks. Untreated control rats consuming regular rat diet (RCD; 11 kcal%) were monitored in parallel. Body weight gain was accelerated in rAAV-GFP + HFD control rats relative to those consuming RCD, despite equivalent kcal consumption. At 9 weeks, serum leptin, free fatty **acids**, triglycerides, and insulin were elevated in HFD control rats. In contrast, rAAV-lep treatment reduced intake and blocked the HFD-induced increase in weight, adiposity, and metabolic variables. Blood glucose was slightly reduced but within the normal range, and serum **ghrelin** levels were significantly elevated in rAAV-lep + HFD rats. Uncoupling protein-1 (UCP1) mRNA in brown adipose tissue (BAT), an index of energy expenditure through nonshivering thermogenesis, was decreased in rats consuming HFD. Treatment with rAAV-lep significantly augmented BAT UCP1 mRNA expression, indicating increased thermogenic energy expenditure. These findings demonstrate that central leptin gene therapy efficiently prevents weight gain, increased adiposity, and hyperinsulinemia in rats consuming an HFD by decreasing energy intake and increasing thermogenic energy expenditure.

L89 ANSWER 3 OF 5 BIOSIS COPYRIGHT (c) 2006 The Thomson Corporation on STN
ACCESSION NUMBER: 2002:396401 BIOSIS <<LOGINID::20060911>>
DOCUMENT NUMBER: PREV200200396401
TITLE: Effects of **ghrelin** injection on blood and body **composition** in rats.
AUTHOR(S): Bohan, Michelle Marie [Reprint author]; Sonon, Roberto; Bobe, Gerd; Lu, Yun; Knight, Travis; Wertz, Aimee; Trenkle, Allen; Beitz, Donald
CORPORATE SOURCE: Biochemistry, Biophysics and Molecular Biology, Iowa State University, 311 Kildee Hall, Ames, IA, 50011, USA
SOURCE: FASEB Journal, (**March 20, 2002**) Vol. 16, No. 4, pp. A619. print.
Meeting Info.: Annual Meeting of the Professional Research Scientists on Experimental Biology. New Orleans, Louisiana, USA. April 20-24, 2002.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Jul 2002
Last Updated on STN: 24 Jul 2002

AB **Ghrelin** has been reported to cause hyperglycemia in humans and adiposity in rodents. The objective of this study was to test the effects of **ghrelin** on blood and body **composition** in rats. Adult male Sprague Dawley rats were administered 2.4 mug/kg **ghrelin** in 0.15 M NaCl or vehicle (0.15 M NaCl) every morning for 30 days. The terminal blood sample was analyzed for glucose, cholesterol, urea nitrogen, and nonesterified fatty **acid** concentrations. The carcasses were analyzed for total lipid and nitrogen content. Blood urea nitrogen, nonesterified fatty **acids**, carcass total lipid, and carcass total nitrogen concentrations were similar for the control and **ghrelin** groups. Blood glucose concentration, however, tended to be higher in the **ghrelin** group than in the control (**ghrelin**=172.32 mg/dl, control=149.72 mg/dl). Blood cholesterol was higher in the **ghrelin** group (**ghrelin**=121.34 mug/ml, control=106.87 mug/ml). **Ghrelin** administered at 2.4 mug/kg did not cause adiposity in rats but did tend to cause hyperglycemia in rats.

L89 ANSWER 4 OF 5 EMBASE COPYRIGHT (c) 2006 Elsevier B.V. All rights reserved on STN
ACCESSION NUMBER: 2002269764 EMBASE <<LOGINID::20060911>>

TITLE: Plasma **ghrelin** levels during exercise in healthy subjects and in growth hormone-deficient patients.
AUTHOR: Dall R.; Kanaley J.; Hansen T.K.; Mooller N.; Christiansen J.S.; Hosoda H.; Kangawa K.; Jorgensen J.O.L.
CORPORATE SOURCE: J.O.L. Jorgensen, Medical Department M, Aarhus Kommunehospital, DK 8000 C, Denmark. jolj@dadlnet.dk
SOURCE: European Journal of Endocrinology, (**2002**) Vol. 147, No. 1, pp. 65-70. .
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AB Objective: To characterise plasma levels of the recently identified endogenous ligand for the GH secretagogue receptor (**ghrelin**) during submaximal aerobic exercise in healthy adults and in GH-deficient adults. Design: Eight healthy males (mean ± S.E. age, 40.8±2.9 years) and eight hypopituitary males with verified GH deficiency (mean ± S.E. age, 40.8 ±4.7 years) underwent a baseline test of their peak aerobic capacity (VO(2) peak) and lactate threshold (LT) on a cycle ergometer, as well as an evaluation of body **composition**. The patients were then studied on two occasions in random order when they exercised for 45 min at their LT. On one occasion, GH replacement had been discontinued from the evening before, whereas on the other occasion they received their evening GH in addition to an intravenous infusion of GH (0.4 IU) during exercise the following day. The healthy subjects exercised ata their LT on one occasion without GH. Results: The patients were significantly more obese and had lower VO(2) max (corrected for body weight) and LT as compared with the control subjects. Exercise induced a peak in serum GH concentrations after 45 min in the control group (11.43±3.61 μg/l). Infusion of GH in the patients resulted in a peak level after 45 min, whereas no increase was detected when exercising without GH (9.77±2.40 (GH) vs 0.11±0.07 μg/l (no GH)). Plasma **ghrelin** levels did not change significantly with time in either study, and no correlations were detected between **ghrelin** levels and parameters such as GH and IGF-I levels, age or body **composition**. Plasma **ghrelin** levels were significantly lower during the study period with GH as compared with the study with no GH. Conclusions: Submaximal aerobic exercise of an intensity sufficient to stimulate GH release was not associated with significant alterations in plasma **ghrelin** concentrations, which indicated that systemic **ghrelin** is not involved in the exercise-induced stimulation of GH secretion. The observation that **ghrelin** levels were lower during GH replacement suggests that GH may feedback-inhibit systemic **ghrelin** release.

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AB Human aging is associated with declining activity of the GH/IGF-I axis and the impressive similarity between consequences of GH deficiency in hypo-pituitary patients and age-related decline in structure functions and metabolism has been pointed out. The neologism somatopause has been therefore coined to indicate the potential link between the age-related decline in GH and IGF-I levels and changes in body **composition**, structure functions and metabolism which connote aging. This assumption led to clinical trials focusing on rhGH and/or rhIGF-I as potential anabolic drug interventions in elderly subjects. To restore the activity of GH/IGF-I axis with anabolic, anti-aging purposes, attention has been also paid to GH-releasing molecules such as GHRH and, particularly, to orally active, synthetic GH Secretagogues (GHS). At present, there is no definitive evidence that frail elderly subjects really benefit from restoring GH and IGF-I levels within the young adult range by treatment with rhGH, rhIGF-I, GHRH or GH Secretagogues. However, GHS would have perspectives as anti-aging intervention not only as function of their stimulatory effect on GH and, in turn, on I-GFI secretion. This evidence comes from studies on synthetic GHS and, more recently, on **ghrelin** , a natural GHS predominantly produced by the stomach. Besides their potent GH-releasing effect, **ghrelin** as well as synthetic GHS has other remarkable GH-independent activities, including (a) stimulation of lactotroph and corticotroph secretion; (b) orexant activity coupled with control of energy expenditure; (c) influence on sleep; (d) control of gastric motility and **acid** secretion; (e) influence on the endocrine pancreatic function and glucose metabolism; (f) cardiovascular actions including protection from ischemia and increase of the cardiac contractility in vivo and antiapoptotic effects in vitro; and (g) anti-proliferative effects in neoplastic thyroid, breast and lung cell lines. It is already clear that **ghrelin** is an hormone signaling the metabolic balance and managing the neuroendocrine and metabolic response to starvation; taking also into account its orexant activity, the potential interest of synthetic GHS acting as agonist or antagonist on the appetite is even obvious and would have perspectives in aging when either overweight or malnutrition are common and imply well-known clinical consequences. Cardiac ischemia and dilated cardiomyopathy are common in aging and the possibility that new GHS analogues are able to protect myocardial and, possibly, endothelial function has to be verified. Attention should be given also to the anti-proliferative effects of GHS analogues devoid of stimulatory effect on the activity of GH/IGF-I axis. In all, there is no present anti-aging drug intervention related to the GH/IGF-I axis; however, potential perspectives would come from orally active GHS not only as function of their stimulatory effect on GH and IGF-I secretion but because of their remarkable GH-inde